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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,006	09/17/2001	Robert J. Schneider	5914-084-999	7849

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EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 12/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,006	SCHNEIDER ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *34-353* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22 and 24-35* is/are pending in the application.

4a) Of the above claim(s) *34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22 and 24-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

This is a response to the amendment, paper No. 16, filed 08/02/04. Claims 22, 24 and 30 have been amended. New claims 31-35 are added. Claims 22 and 24-35 are pending. Claims 22 and 24-33 are considered before the examiner.

Election/Restrictions

Newly submitted claims 34-35 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 34-35 are directed to another method for treating HBV infection comprising administration of a cytosolic calcium inhibitor plus more than one other compound to an HBV-infected patient, which differs for the elected group III, claims 22, and 24-33 drawn to use only one a cytosolic calcium inhibitory compound for treating HBV infection.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 34-35 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Please note any ground of rejection(s) that has not been repeated is removed. Text of those sections of Title 35, U.S. Code not including this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 22 and 24-33 are still rejected under 35 U.S.C. 112, first paragraph on the same ground as stated in the previous Office Action, because the specification, while being enabling

for using an in vitro cell line system to demonstrate that the expression of recombinant hepatitis B virus (HBV) X protein (HBx) in cell line increase the activation of Src family tyrosine kinases, wherein the activation of the kinase, such as Pyk2, can be inhibited by calcium chelator EGTA or calcium channel poison or modulator cyclosporine A (CsA), does not reasonably provide enablement for having an in vivo method for treating patients infected with HBV by using any or all agents, which are able to modulate the cytosolic calcium concentration of a cells in vitro. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to made and use the invention commensurate in scope with these claims.

3. In response to the previous Office Action, Applicants submit amended claims 22, 30 and add new claims 32-33. Then Applicants transverse the rejection based on three main points: (1). Specification provides an in vitro assay for identification of genus compound that is able to reduce cytosolic calcium concentration will inhibit HBV replication. The. In particular, the specification shows that 1 μg/ml of cyclosporin is effective to inhibit HBV replication in cells (see page 82, lines 1-9 of the instant specification as amended, and Figure 10) in vitro, wherein the concentration is effective doses of cyclosporin taught in the specification are within clinically acceptable and safe ranges. (2). There is no animal system were universally accepted an animal models of HBV disease. Instead, cell-bases assays were used as more reliable predictions of efficacy of treating HBV infection. Especially, at the time of the invention, none of the animal systems suggested by the Examiner (woodchuck, mouse, and pecking duck) were universally accepted as animal models of HBV disease. Instead, cell-based assays were used as more reliable predictions of efficacy for treating HBV infection. (3). Applicants emphasize that 35 U.S.C. 112 does not require in vivo testing of the methods encompassed by the claims. In particular, the Federal Circuit has deemed results of in vitro tests sufficient as long as they are reasonably correlated with, without being absolutely predictive of, a pharmacologically useful in vivo response. Fujikawa v. Wattanasin, 93 F.3d 1559, 1564, 39 USPQZd 1895, 1899 (Fed. Cir. 1996).

4. Applicants' argument has been fully considered; however, it is not found persuasive. The case law of Fujikawa v. Wattanasin in MPEP is directed to the situation of written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those

skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967). The current rejection is 112 1st paragraph enablement rejection. As stated in the previous Office Action, the test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosure in the application coupled with information known in the art without undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting 7 factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988).

5. Because the scope of claimed invention is broadly drawn to use any or all cytosolic calcium inhibitor, in view state of art that, some of the cited compounds recognized by the state art produce significant detrimental effects. For example, administration of cyclosporine A in HBV infected patient does produce an unpredictable result as motioned in the previous Office Action. Moreover, some calcium inhibitor as listed in claim 33, as demonstrated by the persons skilled in the art produce significant detrimental effects in vivo. For example, verapamil, a calcium inhibitor, does not inhibit the HBV replication, instead, it exhibits a strong hepatotoxicity, causes liver damage and induces hepatitis (Dr. Kumar. D. in West J. Med. 1994, Vol. 160 (50), pp. 485-486, Dr. Guarascio P. Br. Med. J. 1984, Vol. 288, pp. 362-364, and Dr. Stern et al. N. Engl. J. Med. 1982, Vol. 306, pp. 612-613). Therefore, considering the high unpredictability of using many claimed toxic calcium inhibitor for treating patients, the in vivo data are still required to support the claimed invention.

6. Therefore, the rejection is maintained.

New Ground of Rejections:

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 22-27, and 30-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Frederich et al. (Z. Gastroenterol 1988, Vol. 26, pp. 265-270).

3. Frederich et al. disclose a case report that 20 advanced chronic hepatitis patients, including 9 hepatitis B patients, were treated with cyclosporine A alone (See Summary on page265) . Therefore, the claimed invention is inherently anticipated by the cited prior art.

4. The above rejections are based on the analysis of prior art inherency by Feit et al. (2003, J. Pat. Trade. Off. Soc., Vol. 85, No. 1, pages 5-21). Feit et al. teach three criteria for inherency. (1) The most important criterion is certainty. Citing *In re Tomlinson* and *In re Zierden*, Feit et al. state that certainty is established when the reference process necessarily results in the claimed process as opposed to a possibility. (2) The second criterion is chronology; it will always happen. Feit et al. state that the chronological test is forward chronology. Citing *Eli Lilly and Co. v Barr Laboratories, Inc.*, Feit et al. argue that the claimed result must always be obtained based upon the prior art method. (3) The third criterion is the legal standard. Feit et al., citing *Continental Can,* state that the legal standard is whether the missing descriptive material would be so recognized by a person of ordinary skill in the art as necessarily present in the thing.

5. In the instant case, because the prior art teaches to use structurally and functionally same compound for treating same population of patients having a HBV infection, the inhibition of cytosolic calcium by the compound will certainly, and always happen. Specially, the fact of cyclosporine and nefidipine are known by skill in the art as a calcium inhibitor.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 571-272-0904. The examiner can normally be reached on 7:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bao Qun Li
11/23 2004

James C. Housel 11/29/04